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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,458	09/10/2003	Gary W. Pace	8703-510	7151

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,458	PACE ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 2/29/08.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-37 is/are pending in the application.

4a) Of the above claim(s) 4,6,8,9,12-16 and 20-23 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,5,7,10,11,17-19 and 24-37 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 01 July 2004 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/29/08 has been entered.

Claims 26-37 are new. Claims 1-37 are pending. Claims 4, 6, 8, 9, 12-16 and 20-23 are withdrawn from consideration. Claims 1-3, 5, 7, 10, 11, 17-19 and 24-37 are under examination.

Comment: Applicant asserts that the drawings will corrected at the time of allowance but until that time the drawings shall remain objected.

Withdrawn rejections:

Applicant's amendments and arguments filed 2/29/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Drawings

The drawings are objected to because the legend on the left side of the graph is not legible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate

prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7, 17-19, 24-26, 29-33, 36 and 37 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Ross et al. (Pain 2000, 84, 421-428).

Ross et al. disclose methods of administering sub-analgesic amounts of morphine and oxycodone, in the forms of the hydrochloride salt, to adult rats via intraperitoneal and subcutaneous dosing (Abstract, page 422, 2.2 drugs; 2.4 dosing

regimens). Marked antinociceptive synergy was observed following simultaneous administration of sub-antinociceptive doses of oxycodone and morphine (Page 423, 3. results and page 426, 4. Discussion). It is the Examiner's position that even rats are at risk for respiratory illness such as sleep apnea which can be central, obstructive or mixed sleep apnea. Since any patient even a rat is at risk for a diagnosed or undiagnosed respiratory illness such as sleep apnea which can be central, obstructive or mixed sleep apnea, then the method of reducing the risk associated with the administration of opioid analgesics is inherent in the method of Ross et al. Ross et al. teach icv and subcutaneous injection of the solutions thus reading on instant claims 36 and 37 (page 422). Thus the method disclosed by Ross et al. intrinsically reduces the risk associated with the administration of opioid analgesics in patients and reads on claims 1-3, 7,17-19 and 26. Ross et al. teach dosing ratios of oxycodone to morphine of 25%:75%; 50%:50% or 75%:50% relative to the ED_{50} doses of either morphine or oxycodone as determined in their experiments. These ratios are 1:3; 1:1 and 1.5:1 which read upon *about* 2:3 to *about* 2:1 and *about* 3:2 of instant claims 24, 26 and 33 and is about 2:1 of instant claims 25 and 32 (Page 423, 2.4.4 subcutaneous dosing and page 425, Figures 2 and 3).

Response to arguments:

Applicant admits: "Although the data disclosed in Ross et al., in accord with the Action's characterization, disclose the antinociceptive synergy arising from compositions comprising oxycodone and morphine, it is clear that this result was the sole investigative goal of the work." Applicant continues: "Indeed, the very analgesic synergy disclosed in

the Ross et al. reference would lead one of ordinary skill in the appropriate art to expect a concomitant level of synergy with respect to side effects of this sort. The widely-accepted reference, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th Ed., New York: McGraw-Hill (2001) (as attached to Amendment and Response filed with respect to office Action of 7 February 2007) unequivocally states, on page 579, in the context of the use of mixed opioid compositions to reduce the occurrence of side effects such as respiratory depression, that "for the same degree of analgesia, the same intensity of side effects will occur." (Emphasis added.)". The Examiner simply cannot agree. The citation used by Applicant is reproduced below:

> **Mixed agonist-antagonist compounds were developed for clinical use with the hope that they would have less addictive potential and less respiratory depression than morphine and related drugs. In practice, however, it has turned out that for the same degree of analgesia, the same intensity of side effects will occur. (American Pain Society,**

As is clearly shown, the reference is drawn to the context of mixed agonist-antagonist ***compounds*** and not mixed opioid ***compositions***. Thus, Applicant's arguments are invalid. Moreover, Ross et al. report that co-administration of sub-antinociceptive doses of oxycodone plus morphine produced unexpected antinociceptive synergy with ***a reduced incidence of CNS side effects*** (page 426, Discussion). Thus contrary to Applicant's assertion that the side effects would be commensurate in intensity with the analgesia produced, Ross et al. report reduced side effects.

Applicant asserts that there is nothing disclosed in the reference where it is possible to achieve both analgesia and reduction in respiratory depression and that mass loading of actives is different from the instant invention. The Examiner cannot agree. Claim langauge is controlling and the ratio of components taught by Ross et al. embrace those instantly claimed. Applicant's arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

Claims 1-3, 5, 7, 10, 11, 17-19 and 24-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. (WO 97/14438).

Smith et al. disclose methods of producing analgesia in humans and lower animals which comprising administering sub-analgesic dosages of morphine and oxycodone and their pharmaceutically acceptable salts (Claim 23-25 and 28). Smith et al. also disclose hydromorphone (Claim 24 and 27). The route of administration can be subcutaneous, intravenous, intramuscular, buccal, sublingual, oral or rectal, for example and reads on claims 10 and 34-37(Claims 30-35 and 44, for example). Intravenous would mean a solution and subcutaneous would mean injectable formulation thus anticipating instant claims 36 and 37. The analgesic composition can be administered in oral slow- or controlled release dosage form and thus reads on instant claims 11 (claims 44 and 46). It is the Examiner's position, in the absence of evidence to the contrary, that Smith et al. make the distinction between immediate release oral dosing and sustained release oral dosing in claims 44 and 46 and thus reads on instant claims 10, 27, 28 and

34. Since any patient is at risk for a diagnosed or undiagnosed respiratory illness such as sleep apnea which can be central, obstructive or mixed sleep apnea, then the method of reducing the risk associated with the administration of opioid analgesics is inherent in the method of Smith et al. thus reading on instant claims 17-19, 26, 29, 30 and 31. Smith et al. disclose a wide range of dosing regimens, which the Examiner interprets to read on instant claims 8, 9, 24 and 25 (Claims 25-43). Thus, instant claims 1-3, 5, 7, 10, 11, 17-19 and 24-37 are fairly anticipated by Smith et al.

Response to arguments:

Applicant continues the assertion that the accepted wisdom in the art was that any composition displaying an increased analgesic effect would also display an accompanying increase in undesirable side effects. This is simply wrong as clearly shown by the Examiner in the response to arguments above. Applicants arguments are not persuasive.

Claim Rejections - 35 USC § 102

Claims 1-3, 5, 7, 10, 11, 17-19 and 24-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. (US 6,310,072).

Smith et al. disclose

72. A method for producing analgesia in humans and lower animals which comprises administering concurrently to a human or lower animal in need of such treatment a composition comprising a sub-analgesic dosage of a μ-opioid agonist selected from the group consisting of morphine, fentanyl, sufentanil, alfentanil and hydromorphone, or a pharmaceutically acceptable salt thereof, and a sub-analgesic dosage of oxycodone which is a κ_2-opioid agonist or a pharmaceutically acceptable salt thereof.

73. A method as claimed in claim 72 wherein the μ-opioid agonist is in the form of a pharmaceutically acceptable salt.

74. A method as claimed in claim 72 wherein the μ-opioid agonist is morphine.

Since any patient is at risk for a diagnosed or undiagnosed respiratory illness such as sleep apnea which can be central, obstructive or mixed sleep apnea, then the method of reducing the risk associated with the administration of opioid analgesics is inherent in the method of Smith et al. thus reading on instant claims 1-3, 5, 7 and 17-19 and 29-31.

Smith et al. disclose

mg/kg and about 5 mg/kg every three to six hours.

143. A method as claimed in claim 72 wherein the mode of administering the composition is selected from the group consisting of oral, rectal, parenteral, sublingual, buccal, intrathecal, epidural, intravenous, intra-articular, intramuscular, intradermal, subcutaneous, inhalational, intraocular, intraperitoneal, intracerebroventricular and transdermal.

thus anticipating instant claims 34-37.

Smith et al. disclose various administration routes and controlled-release dosage forms reading on instant claim 11 (see claim 155). It is the Examiner's position, in the absence of evidence to the contrary, that Smith et al. make the distinction between immediate release oral dosing and sustained release oral dosing and thus reads on instant claim 10 and 26-28.

Smith et al. disclose a wide range of dosages in claims 72-145 reading on instant claims 26, 32 and 33.

Response to arguments:

The same argument is applicable here as above since Smith et al. (WO '438) is the foreign counterpart to Smith et al. (US '072) and they share a common disclosure and the arguments are the same.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Examiner, Art Unit 1616